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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,701	09/24/2003	Xing Su	21058/0206508-US0	8780

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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,701	SU ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007 and 11 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7 and 9-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 9-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/30/07 has been entered.

2. As noted below, this application is currently being examined by a different examiner.

3. Applicant's amendments to claims 1 and 12 in the reply filed on 11/30/07, and cancellation of claims 15-26 in the reply filed on 1/11/08 are acknowledged.

4. Applicant's arguments, filed 11/30/07, with respect to the following rejection(s):

   a. Claims 1-3, 5, 7, 9-26 rejected under 35 U.S.C. 103(a) - Cleve et al (Mol. Cell. Probes (1998) 12:243-147) in view of Dimitrov et al (U.S. PgPub 2003/0013091).

   b. Claims 1-3, 5, 7, 9-26 rejected under 35 U.S.C. 103(a) - Singer et al (U.S. Patent 6,534,266)in view of Urdea et al (U.S. Patent 5,635,352) and further in view of Horn et al (U.S. 2001/0009760).

have been fully considered and are persuasive in view of the amendments. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Su et al. (US 7,019,828).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-3, 5, 7, and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleve et al (Mol. Cell. Probes (1998) 12:243-147) in view of Dimitrov et al (U.S. 2003/0013091), and further in view of Su et al. (US 7,019,828).

Cleve teaches a method of claims 1 and 12 comprising: (a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see page 245, columns 1 and 2, where the branched DNA amplifier molecule has 15 branches with four copies of a sequence which bind to labeled probes, where binding of the labeled probes will result in two or more tags attached in a noncovalent manner to an organic molecule backbone), (b) binding the barcode to a target (see page 245, column 2,

where the probes are hybridized to a target), (C) detecting the barcode bound to the target (see page 246, subheading "Flow Cytometry", where the barcodes are individually detected). Wherein the organic molecule backbone comprises one or more branched nucleic acids (see page 245, column 1 and 2, where branched nucleic acids with 15 branches are used which are organic molecules) and the barcode is detected by a technique of fluorescence spectroscopy (see figure 1, and page 246, column 1, where fluorescence spectroscopy is used to measure the beads).

With regard to claims 2-3, Cleve teaches single stranded nucleic acid probes (see page 245, columns 1 and 2, where the probes are single stranded).

With regard to claim 5, Cleve teaches the use of a fluorescent dye such as fluorescein (see page 246, column 2, where fluorescein is, of course, a fluorescent dye, but also will function as a Raman tag).

With regard to claim 7, Cleve teaches branched nucleic acids where the branches are at predetermined locations on the backbone (see page 245, columns 1 and 2).

With regard to claim 9, Cleve teaches that the barcode binds via the oligonucleotide probe (see page 245, column 2).

With regard to claims 11, 13, and 14, Cleve teaches a nucleic acid target and .detection of the binding to the target (see page 245, column 2).

Cleve does not teach the use of a plurality of barcodes on the branched DNA nor the situation where the number of barcodes exceeds the number of different types of tags.

Dimitrov expressly teaches the use of a plurality of barcodes since Dimitrov teaches that "Several unique combinations of labels can be formed using branched nucleic acids (see page 7, paragraph 0057)." Dimitrov further notes that "nucleic acids labeled with any or all of these combinations can be bound to another nucleic acid through hybridization (see page 7, paragraph 0055)."

Dimitrov further teaches the situation where the number of barcodes exceeds the number of different types of tags. Dimitrov expressly states "In this invention, various ratios of different label monomers bound to nucleic acids can be combined to generate a diverse population of unique labels that can include up to 1017 or more unique labels. For example, a nucleic acid labeled with two fluorescein labeled nucleotides and three rhodamine labeled nucleotides will emit light at a different wavelength compared to a nucleic acid labeled with three fluorescein nucleotides and two rhodamine nucleotides. In another example, a nucleic acid could be labeled with different ratios of three or more.label monomer:nucleotides which greatly increases the variety of unique labels that can be generated" (see paragraph 0065). So Dimitrov expressly teaches the situation where ratios of different labels are combined to provide a much larger number of different tags. Dimitrov recognizes that up to 10^{17} or more unique labels can be formed by the use of ratios of a much small number of labels.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cleve to use the multi fluor branched DNA labels of Dimitrov since Cleve expressly motivates the use of different colors, stating "In addition, the principle of FCM quantitation can be expanded to take

advantage of the technology's unique strengths: through the use of software tools, beads of different colours or different sizes can be quantitated separately" (see page 244, column 1). Thus, Cleve directly motivates the use of different colors in the analysis assay and Dimitrov addresses this ability with the branched DNA-labels that can differ in color to "provide an accurate and sensitive system for the detection and quantitation of analytes in a mixture (see page 2, paragraph 10)." An ordinary practitioner would have been motivated to use the multifluor branched DNA probes of Dimitrov in the branched DNA assay of Cleve in order to permit multiplex detection of different analytes in a mixture as taught by Dimitrov and as motivated by Cleve, who desired to detect both HIV and cytomegalovirus (see page 2471 column 1, for example) in a single reaction.

Cleve also does not discuss the use of a signal enhancing surface comprising a salt located in proximity to the barcodes.

Su et al. teach the use of lithium chloride in close proximity (i.e. on a surface proximately located) to increase the intensity of signals from SERS in detecting nucleic acids (see abstract and claims 6, 15-16). Su states that "the probability of Raman interaction occurring between an excitatory light beam and an individual molecule in a sample is very low, resulting in low sensitivity and limited applicability of Raman analysis" (col.1, lines 37-40). The placement of various activators near the labels "can function to enhance the localized effects of electromagnetic radiation," and "molecules (i.e. analytes of interest) located in the vicinity of such [activators] exhibit much greater sensitivity for Raman Spectroscopic analysis" (col.1, lines 50-53).

One of ordinary skill in the art would have been motivated to further modify the method of Cleve et al. to use a signal enhancing surface proximately located to the barcodes, comprising two or more different types of tags (i.e. fluorescein, which also functions as a Raman tag), of Cleve because Su et al. state that the use of various salts, specifically, sodium chloride was known in the art at the time of the invention to enhance the signal of Raman tags when applied to proximately located surfaces (col.1, lines 65-67), and further demonstrates the benefits of using another salt, lithium chloride, as another enhancer which is more sensitive in detecting lower concentrations of target molecules (col.2, lines 2-5). Furthermore, Su specifically suggests that the use of LiCl may be applied to the design and selection of tag molecules that can provide strong SERS signals (col.6, lines 58-60). Therefore, the skilled artisan would have had a reasonable expectation of success in using a signal enhancing surface proximately located to the barcodes of Cleve et al. for the purpose of enhancing the signal from the two or more different types of tags located on the barcodes in order to provide a more sensitive detection of the target molecule. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed signal enhancing surface therein.

8. Claims 1-3, 5, 7, 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al (U.S. Patent 6,534,266) in view of Urdea et al (UIS. Patent 5,635,352), in view of Horn et al (U.S. 2001/0009760), and further in view of Su et al. (US 7,019,828).

Singer teaches a method of claims 1 and 12 comprising: (a) obtaining a plurality of barcodes, at least one of the plurality of barcodes comprising two or more different tags attached to an organic molecule backbone (see column 8, lines 6-38, where oligonucleotides have five different fluorophores attached to the nucleic acid probe backbone to form 31 different barcodes), (b) binding at least one of the plurality of barcodes to a target (see column 8, • lines 39-43, where the probes are hybridized to a target), (c) detecting at least one of the plurality of barcodes bound to the target (see column 8, lines 44-57, where the barcodes are individually detected). Wherein the barcodes are detected by fluorescence spectroscopy (see column 9, lines 5-20) and wherein the number of barcodes in the plurality of barcodes exceed the number of different types of tags attached to the plurality of barcodes (see column 8, lines 16-24, "Using a total of five spectrally distinguishable fluorochromes, 31 different bar codes are created without using a given fluorochrome more than once in a given bar code. The creation of the 31 bar codes using 5 fluorochromes is an extension of the scheme illustrated in FIG. 1, where 15 qualitative bar codes are created using 4 fluorochromes. One of the 31 bar codes is assigned to each of the 31 target sequences.").

With regard to claims 2-3, Singer teaches single stranded nucleic acid probes (see column 8, lines 16-38, where the oligonucleotides were synthesized, which necessarily is single stranded).

With regard to claim 5, Singer teaches the use of a variety of fluorescent dyes such as Cy3, Cy5, etc (see column 3, lines 1-2, where these dyes are, of course, fluorescent dyes, but also will function as Raman tags).

With regard to claim 9, Singer teaches that the barcode binds via the oligonucleotide probe (see column 8, lines 39-43).

With regard to claim 10, Singer teaches that distinguishable barcodes can be generated using multiple copies of the same tag (see column 3, line 59 to column 4, line 6).

With regard to claims 11, 13, and 14, Singer teaches a nucleic acid target and detection of the binding to the target (see column 8, lines 39-57).

Singer does not teach the use of branched DNA probes.

Urdea teaches a method of claims 1 and 12 comprising: (a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see figure 11 and column 20, line 35 to column 21, line 49, where the AMP or comb probe is formed by the attachment of branches of nucleotides, and where 14 different tags are attached to the nucleic acid backbone (see column 20, line 38, specifically)), (b) binding the barcode to a target (see figure 11 and column 21, line 50 to column 22, line 7, wherethe probes are hybridized to a target), (c) detecting the barcode bound to the target (see figure 11 and column 22, lines 8-20, where the barcodes are detected).

With regard to claims 2-3, Urdea teaches single stranded nucleic acid probes (see figure 11 and column 20, line 35 to column 21, line 37, where the oligonucleotides were synthesized, and shown as single stranded).

With regard to claim 5, urdea teaches the use of nucleotide tags which are detected (see figure 11 and columns 20-22).

With regard to claims 6-7, Urdea teaches branched nucleic acids with branches located at predetermined sites along the backbone (see figure 11 and column 20, line 35 to column 21, line 40).

With regard to claim 9, Urdea teaches that the barcode binds via the oligonucleotide probe (see figure 11 and Column 21, line 50 to column 22, line 7).

With regard to claim 10, Urdea teaches that distinguishable barcodes can be generated using multiple copies of the same tag (see figure 13, where binding of AMP 1 and AMP2 can be distinguished by LP1 and LP2).

With regard to claims 11, 13, 14, Urdea teaches a nucleic acid target and detection of the binding to the target (see figures 11 and 13 and column 21, line 50 to column 22, line 7).

With regard to claim 12, Urdea teaches a "container" and "probe section" where the tagged LP1 and LP2 probes are hybridized to the AMP probes to create a barcode (see figure 13).

Horn provides a specific motivation to apply the branched DNA (or bDNA) method of Urdea to in situ hybridization methods such as those of Singer (see paragraph 0110-0111).

It would have been prima facie obvious to one of ordinary skill in the art at the. time the invention was made to modify the method of Singer to use the sensitive branched DNA probes of Urdea as motivated by Urdea and Horn since Singer recognizes a need for sensitive detection, noting "An imaging technology, preferred for sensitive, quantitative detection of fluorochromes is described in Femino (see column 6,

lines 32-34). Urdea notes regarding Branched DNA probes that "The invention increases both the sensitivity and specificity of such assays, by reducing the incidence of signal generation that occurs in the absence of target, and does not involve a substantial increase in either time or cost relative to current assay configurations (see column 2, lines 46-51)." Consequently, Urdea informs the ordinary practitioner that branched DNA probes are desirable for a number of reasons including sensitivity and specificity and reduction in nonspecific signal and these are elements of interest to Singer, who is interested in sensitive quantitative detection in an in situ assay. Horn specifically motivates the use of branched DNA probes in *in situ* assays such as those employed by Singer, noting "These results demonstrate the usefulness of bDNA in mapping small regions of DNA on a large backbone. Not only was the time to completion greatly shortened using bDNA (1 day or less) but the fluorescence signal using bDNA was considerably higher (see paragraph 0111)." So an ordinary practitioner, interested in sensitive detection using the bar code method of Singer, would have been motivated to further amplify the signal of the bar codes with branched DNA since Urdea indicated that branched DNA improved sensitivity and Horn expressly indicates that branched DNA use in *in situ* hybridization assays shortened the time to completion while also providing considerably greater fluorescence signal.

Singer also does not discuss the use of a signal enhancing surface comprising a salt located in proximity to the barcodes.

Su et al. teach the use of lithium chloride in close proximity (i.e. on a surface proximately located) to increase the intensity of signals from SERS in detecting nucleic

acids (see abstract and claims 6, 15-16). Su states that "the probability of Raman interaction occurring between an excitatory light beam and an individual molecule in a sample is very low, resulting in low sensitivity and limited applicability of Raman analysis" (col.1, lines 37-40). The placement of various activators near the labels "can function to enhance the localized effects of electromagnetic radiation," and "molecules (i.e. analytes of interest) located in the vicinity of such [activators] exhibit much greater sensitivity for Raman Spectroscopic analysis" (col.1, lines 50-53).

One of ordinary skill in the art would have been motivated to further modify the method of Singer et al. to use a signal enhancing surface proximately located to the barcodes, comprising two or more different types of tags (i.e. fluorphores, which also function as Raman tags), of Singer because Su et al. state that the use of various salts, specifically, sodium chloride was known in the art at the time of the invention to enhance the signal of Raman tags when applied to proximately located surfaces (col.1, lines 65-67), and further demonstrates the benefits of using another salt, lithium chloride, as another enhancer which is more sensitive in detecting lower concentrations of target molecules (col.2, lines 2-5). Furthermore, Su specifically suggests that the use of LiCl may be applied to the design and selection of tag molecules that can provide strong SERS signals (col.6, lines 58-60). Therefore, the skilled artisan would have had a reasonable expectation of success in using a signal enhancing surface proximately located to the barcodes of Singer et al. for the purpose of enhancing the signal from the two or more different types of tags located on the barcodes in order to provide a more sensitive detection of the target molecule. It would have been *prima facie* obvious to

one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed signal enhancing surface therein.

Summary

9. No claims are free of the prior art.

10. Chan et al. (US 2004/0110208) and Mirkin et al. (US 2003/0211488) are noted as references of interest.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 1/30/08

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/30/08